Synthesis of Xanthines by Cyclization of the Michael-type Adducts from 6-Aminouracils and Diethyl Azodiformate

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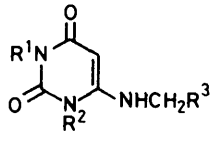
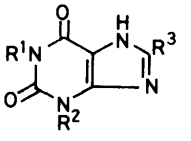
Treatment of the Michael-type adducts from 6-alkylamino-1,3-dimethyluracils and diethyl azodiformate (DAD) with oxidizing agents such as nitrobenzene, lead tetra-acetate, and lead dioxide as well as DAD itself caused dehydrogenation, followed by thermal cyclization, to give the corresponding theophyllines. Treatment of 6-alkylaminouracils with an excess of DAD gave directly the corresponding xanthine derivatives. Reactions of 6-amino-5-(1,2-bisethoxycarbonylhydrazino)-1,3-dimethyluracil with aromatic aldehydes and with dimethylformamide diethyl acetal gave the corresponding 8-arylheophyllines and 8-dimethylaminotheophylline, respectively.

PREVIOUS papers have reported some new synthetic routes to isoalloxazines, alloxazines, toxoflavins, and



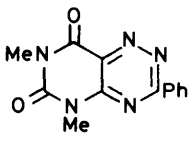
(1) a; $R^1 = R^2 = Me$, $R^3 = Ph$
b; $R^1 = R^2 = Me$, $R^3 = CH_2Ph$
c; $R^1 = Me$, $R^2 = H$, $R^3 = Ph$
d; $R^1 = H$, $R^2 = Me$, $R^3 = Ph$
e; $R^1 = R^2 = Me$, $R^3 = Et$
f; $R^1 = R^2 = Me$, $R^3 = Pr^n$



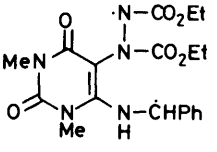
(2) a; $R^1 = R^2 = Me$, $R^3 = Ph$
b; $R^1 = R^2 = Me$, $R^3 = CH_2Ph$
c; $R^1 = Me$, $R^2 = H$, $R^3 = Ph$
d; $R^1 = H$, $R^2 = Me$, $R^3 = Ph$
e; $R^1 = R^2 = Me$, $R^3 = Et$
f; $R^1 = R^2 = Me$, $R^3 = Pr^n$
g; $R^1 = R^2 = Me$, $R^3 = p\text{-}ClC_6H_4$
h; $R^1 = R^2 = Me$, $R^3 = p\text{-}MeOC_6H_4$
i; $R^1 = R^2 = Me$, $R^3 = p\text{-}NO_2C_6H_4$
j; $R^1 = R^2 = Me$, $R^3 = 3,4\text{-}Cl_2C_6H_3$
k; $R^1 = R^2 = Me$, $R^3 = 3,4(CH_2O_2)C_6H_3$

fervenulins by oxidative cyclization of the Michael-type adducts from 6-aminopyrimidines and diethyl azodiformate (DAD) or 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD).[1,2] The present paper describes a new synthesis of xanthines in which DAD is an effective source of N-7 of the purine ring system.[3]

Treatment of 6-benzylamino-1,3-dimethyluracil (1a)[4] with 1 equiv. of DAD in chlorobenzene gave 6-benzylamino-5-(1,2-bisethoxycarbonylhydrazino)-1,3-dimethyluracil (3a). Heating the product (3a) in nitrobenzene (as oxidizing agent), followed by dilution with ethanol, caused separation of 8-phenyltheophylline (2a)[4] in high yield. Similarly, heating 5-(1,2-bisethoxycarbonylhydrazino)-1,3-dimethyl-6-phenethylaminouracil (3b), prepared from 1,3-dimethyl-6-phenethylaminouracil (1b)[4] and DAD, in nitrobenzene gave 8-benzyltheophylline (2b).[4] Treatment of (3a) with lead tetra-acetate or lead dioxide under reflux in chlorobenzene also gave (2a), in lower yields. In the case of the reaction with lead dioxide, a trace of the pyrimidotriazine (4)[5] was obtained as a by-product. The formation of (4) can be explained by intramolecular coupling of a presumed diradical intermediate (5), followed by hydrolysis by



(4)



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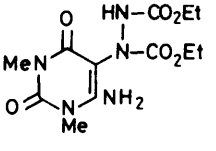

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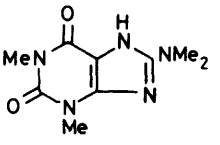

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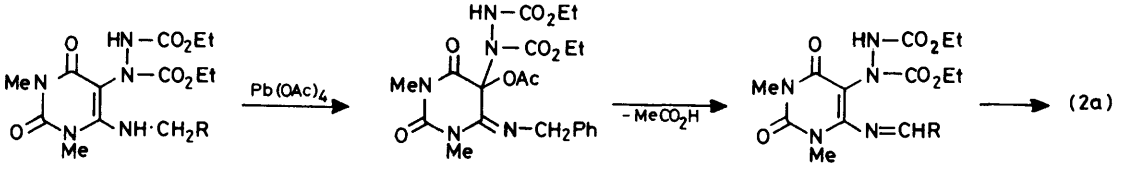


(3) a; R = Ph
b; R = CH_2Ph

(6)

(7) R = Ph
(9) R = NMe_2

(2a)

SCHEME 1

[1] F. Yoneda, S. Matsumoto, Y. Sakuma, and S. Fukazawa, *J.C.S. Perkin I*, 1975, 1907.
[2] F. Yoneda, Y. Sakuma, T. Nagamatsu, and S. Mizumoto, *J.C.S. Perkin I*, 1976, 2398.
[3] Preliminary report, F. Yoneda, S. Matsumoto, and M. Higuchi, *J.C.S. Chem. Comm.*, 1975, 146.
[4] H. Goldner, G. Dietz, and E. Carstens, *Annalen*, 1966, **691**, 142.
[5] (*a*) F. Yoneda, K. Kanahori, and S. Nishigaki, *J. Heterocyclic Chem.*, 1971, **8**, 523; (*b*) F. Yoneda, K. Ogiwara, M. Kanahori, S. Nishigaki, and E. C. Taylor, in 'Chemistry and Biology of Pteridines,' ed. K. Iwai, M. Akino, M. Goto, and Y. Iwanami, International Academic Printing Co. Ltd., Tokyo, 1970, p. 145.

adventitious water, decarboxylation, and aromatization.

In order to clarify the reaction mechanism, the oxidation of (3a) with lead tetra-acetate was studied more carefully. Treatment of (3a) with lead tetra-acetate in dioxan at 50 °C for 4 h gave 5-acetoxy-6-benzylimino-5-(1,2-bisethoxycarbonylhydrazino)-1,3-dimethyluracil (6), identified by elemental analysis, molecular weight (mass spectrometry) and n.m.r. spectra (see Experimental section). Heating compound (6) in tetramethylene sulphone at 200 °C for 4 h afforded (2a) in good yield. The above reaction probably proceeds *via* the intermediate 6-benzylideneaminouracil (7) resulting from elimination of acetic acid.

Treatment of (1a) with 3 equiv. of DAD at 180 °C gave a high yield of (2a) in a single step. The reaction is equally applicable to other 6-alkylaminouracils (1b—f),[4] giving the corresponding xanthines (2b—f)[6] (Table 1).

TABLE 1

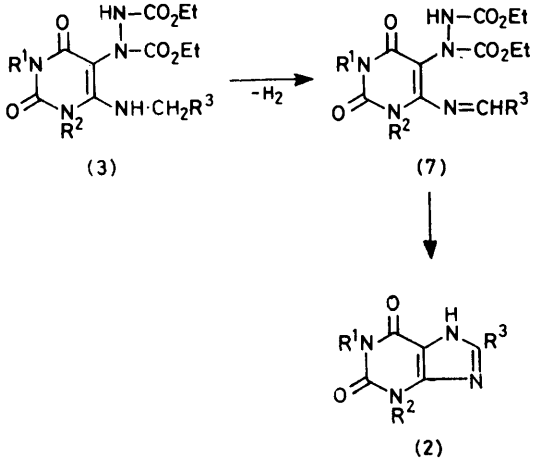
Xanthines by reaction of 6-alkylaminouracils with DAD

Starting material	Temp. (°C)	Time (h)	Product	Yield (%)	M.p. (°C)
(1a)	180	2	(2a) [a]	71	>360
(1b)	180	3	(2b) [a]	70	298
(1c)	180	2	(2c) [a]	68	>360
(1d)	180	2	(2a) [a]	83	>360
(1e)	190	2	(2e) [a]	50	277
(1f)	200	3	(2f) [a]	30	265

[a] Ref. 4.

It is apparent that DAD acts as a dehydrogenation reagent as well as a nitrogen source for the direct cyclization of (1a—f), because treatment of (3a) with further DAD at 170 °C gave (2a). However, the adduct (3a) did not give (2a) on heating or on refluxing in solvents without DAD under any conditions.

The above results indicate that the oxidizing agents abstract two hydrogen atoms from the Michael-type adducts to give 6-anil intermediates (7), which can cyclize to the corresponding xanthine derivatives (2) (Scheme 2). To confirm this mechanism, we have



SCHEME 2

examined the condensation of 6-amino-5-(1,2-bisethoxycarbonylhydrazino)-1,3-dimethyluracil (8) with aromatic aldehydes, which we expected to give intermediates of type (7). Thus heating (8) with several aldehydes at 170—180 °C for *ca.* 4 h yielded the corresponding theophylline derivatives (2a and g—k) (Table 2).

TABLE 2

Theophyllines by reaction of compound (9) with aldehydes

Aldehyde	Temp. (°C)	Time (h)	Product [a]	Yield (%)
Benzaldehyde	170	4	(2a) [b]	72
p-Chlorobenzaldehyde	170	4	(2g) [c]	78
p-Anisaldehyde	170	4	(2h) [c]	65
p-Nitrobenzaldehyde	180	5	(2i)	61
3,4-Dichlorobenzaldehyde	180	3.5	(2j) [c]	82
Piperonal	170	4	(2k)	73

[a] None of these compounds melted below 360 °C. [b] Ref. 4. [c] Ref. 6.

Although the anil intermediates (7) could not be isolated, the following reaction appears to support this mechanism. Refluxing the adduct (8) with dimethylformamide diethyl acetal in ethanol gave the corresponding anil (9) in high yield. Fusion of (9) at 200 °C readily afforded 8-dimethylaminotheophylline (10).[7]

EXPERIMENTAL

M.p.s were obtained with a Yanagimoto micro-apparatus. N.m.r. spectra were determined with a JEOL JNM 3H-60 spectrometer (tetramethylsilane as internal standard) and i.r. spectra (Nujol mulls) with a JASCO IRA-1 spectrometer.

6-Benzylamino-5-(1,2-bisethoxycarbonylhydrazino)-1,3-dimethyluracil (3a).—A mixture of 6-benzylamino-1,3-dimethyluracil (1a) (1.22 g, 0.005 mol) and DAD (0.96 g, 0.0055 mol) was heated at 160 °C for 1 h, then crushed in ether. The crystals were filtered off and recrystallized from ethanol to give *needles* (1.78 g, 85%), m.p. 158°, M^+ 419, $\nu_{max.}$ (Nujol) 3 295, 3 217, 1 738, 1 714, 1 702, 1 620, 1 529, and 1 500 cm^{-1} (Found: C, 54.25; H, 5.8; N, 16.45. $C_{19}H_{25}N_5O_6$ requires C, 54.4; H, 6.0; N, 16.7%).

5-Acetoxy-6-benzylimino-5-(1,2-bisethoxycarbonylhydrazino)-1,3-dimethyluracil (6).—To a solution of the adduct (3a) (1.0 g, 0.0023 mol) in dioxan (20 ml) was added lead tetra-acetate (2.1 g, 0.0047 mol). The mixture was warmed at 55 °C for 4 h then filtered, and the filtrate was diluted with water (80 ml) and set aside for several days. The crystals which separated were filtered off and dried. Recrystallization from ethanol gave *prisms* (0.69 g, 70%), m.p. 178°, M^+ 479, $\nu_{max.}$ (Nujol) 3 170, 1 766, 1 745, 1 722, 1 686, and 1 641 cm^{-1}, δ [$(CD_3)_2SO$] 0.77 (t, *J* 7 Hz, $MeCH_2$), 1.24 (t, *J* 7 Hz, $MeCH_2$), 1.98 (s, Ac), 3.08 (s, NMe), 3.18 (s, NMe), 3.72 (q, *J* 7 Hz, $MeCH_2$), 4.12 (q, *J* 7 Hz, $MeCH_2$), 6.48 (s, $PhCH_2$), and 7.03 (s, ArH) (Found: C, 52.35; H, 6.25; N, 14.55. $C_{21}H_{29}N_5O_8$ requires C, 52.6; H, 6.1; N, 14.6%).

8-Phenyltheophylline (2a).—*Method A.* The hydrazone (6) (0.3 g, 0.0007 mol) was heated in tetramethylene sulphone (2 ml) at 200 °C for 4 h. The solution was evaporated to dryness and the residue was treated with a small amount of water to cause separation of crystals. Recrystallization from dimethylformamide gave (2a) (0.14 g, 76%), m.p. >360°.

Method B. The adduct (3a) (0.6 g, 0.0014 mol) was heated in nitrobenzene (3 ml) at 220 °C for 3 h. After

[6] F. Yoneda and T. Nagamatsu, *J.C.S. Perkin I*, 1976, 1547.
[7] F. Yoneda, M. Higuchi, T. Matsumura, and K. Senga, *Bull. Chem. Soc. Japan*, 1973, **46**, 1836.

cooling, the crystals which had separated were filtered off, washed with ethanol, and recrystallized from dimethylformamide to give (2a) (0.3 g, 83%), m.p. >360°.

Method C. To a solution of the adduct (3a) (1 g, 0.0023 mol) in chlorobenzene (50 ml) was added lead dioxide (1.7 g, 0.007 mol) and the mixture was refluxed for 4 h. After filtration while warm, the solution was set aside overnight to deposit (2a) (0.16 g, 26%), m.p. >360°. After (2a) had been filtered off, the filtrate was set aside for several days to precipitate a trace of 5,7-dimethyl-3-phenylpyrimido[4,5-*e*]-1,2,4-triazine-6,8(5*H*,7*H*)-dione (4) (10 mg), m.p. 239°, identical with an authentic sample.[4]

5-(1,2-*Bisethoxycarbonylhydrazino*)-1,3-*dimethyl*-6-*phenethylaminouracil* (3b).—A mixture of 6-phenethylamino-1,3-dimethyluracil (1b) (1.3 g, 0.005 mol) and DAD (0.96 g, 0.0055 mol) in chlorobenzene (10 ml) was refluxed for 5 h. After cooling, the crystals were filtered off, washed with ether, and recrystallized from ethanol to give *needles* (1.62 g, 75%), m.p. 149°, M^+ 433 (Found: C, 55.65; H, 6.25; N, 15.85. $C_{20}H_{27}N_5O_6$ requires C, 55.4; H, 6.3; N, 16.15%).

8-*Benzyltheophylline* (2b).—The adduct (3b) (0.6 g, 0.0014 mol) was heated in nitrobenzene (3 ml) at 220 °C for 5 h. The mixture was then diluted with ethanol and set aside overnight. The crystals were filtered off and recrystallized from ethanol to give needles (0.3 g, 80%), m.p. 298°.

8-*Arylxanthine Derivatives* (2a—f); *General Procedure.*—A mixture of a 6-alkylaminouracil (1a—f) (0.01 mol) and DAD (0.03 mol) was heated at 180—200 °C for 2—3 h. After cooling, the mixture was crushed in ethanol and the crystals were filtered off and recrystallized from dimethylformamide to give needles (Table 1).

Synthesis of 8-*Aryltheophyllines* (2a *and* g—k) *by Condensation of* 6-*Amino*-5-(1,2-*bisethoxycarbonylhydrazino*)-1,3-*dimethyluracil* (8) *with Aromatic Aldehydes; General Procedure.*—A mixture of (8) (0.01 mol) and an aromatic aldehyde (0.02—0.03 mol) was heated at 170—180 °C for 3.5—5 h, cooled, diluted with ethanol, and set aside overnight. The crystals were filtered off and recrystallized from dimethylformamide (Table 2) [(2i) (Found: C, 51.75; H, 3.6; N, 23.05. $C_{13}H_{11}N_5O_4$ requires C, 51.85; H, 3.7; N, 23.25); (2k) (Found: C, 56.15; H, 4.05; N, 18.7. $C_{14}H_{12}N_4O_4$ requires C, 56.0; H, 4.05; N, 18.65%)].

5-(1,2-*Bisethoxycarbonylhydrazino*)-6-*dimethylaminomethyleneamino*-1,3-*dimethyluracil* (9).—A solution of the adduct (8) (2.6 g, 0.0079 mol) and dimethylformamide diethyl acetal (3.5 g, 0.024 mol) in ethanol (10 ml) was refluxed for 4 h and set aside overnight. The crystals were filtered off and recrystallized from ethanol to give *prisms*, m.p. 125°, M^+ 384 (Found: C, 47.0; H, 6.4; N, 21.9. $C_{15}H_{24}N_6O_6$ requires C, 46.85; H, 6.3; N, 21.55%).

8-*Dimethylaminotheophylline* (10).—The anil (9) (0.5 g, 0.013 mol) was heated at 230 °C for 5 min then set aside at room temperature. The crystals which separated were crushed in ethanol, then filtered off and recrystallized from dimethylformamide to give (10) (0.2 g, 69%), m.p. >330°.

We thank the Ministry of Education of Japan for financial support.

[7/220 *Received*, 8*th February*, 1977]